Animal Models in Preclinical Nutrition Research

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Disclosures:

GAC is employed by The Jackson Laboratory

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Animal Models in Preclinical Nutrition Research

What are animal models and why do we need them?

Human studies are not sufficient
There are no good replacements for animal models

Strengths and limitations of existing animal models.

Mice are not humans
Mice and humans share the same basic biology

How can we do better?

Improved study designs
Animals models that are “more like” humans

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Animal Models in Preclinical Nutrition Research

Statistical Design

sample selection, randomization
power and sample size

The Standardization Fallacy

repetition, replication, and generalization (translation)

standardization → specificity and precision
heterogenization → generalization and accuracy

use animals of both sexes!
use aged animals
introduce genetic diversity
vary diets, environments, and exposures

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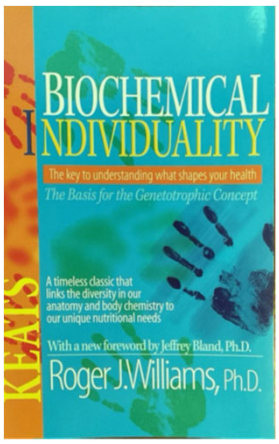
Animal Models in Preclinical Nutrition Research

No two humans are exactly alike due to unique life histories and genetics.

The perfect diet, if it exists, would be different for everyone and would change through the course of life.

To build better animal models for nutrition research we need to acknowledge the biochemical individuality of humans (and mice).



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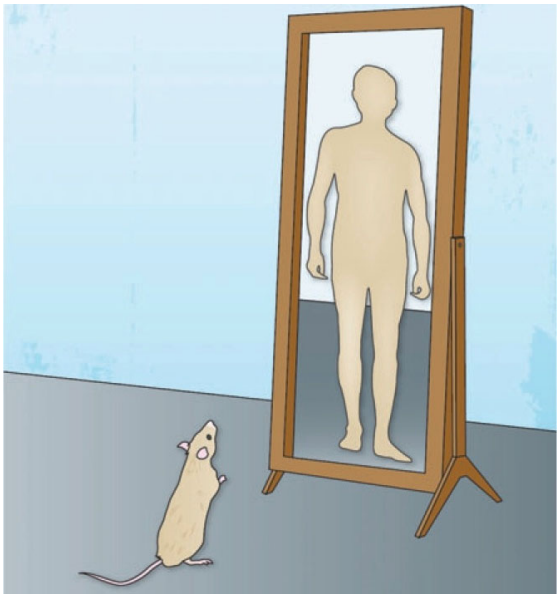
Which mouse is most like a human?



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Which mouse is most like a human?

=

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Which mouse is most like a human?

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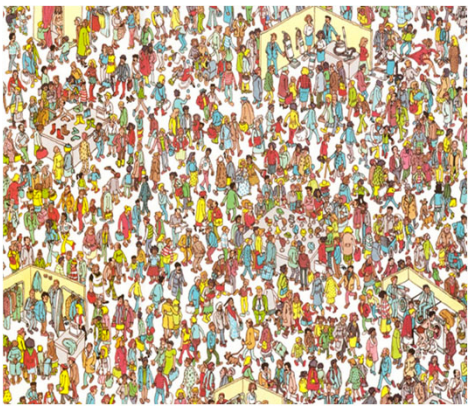

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The Three Bears: a T2D Model

Baker et al, 2025 BioRxiv

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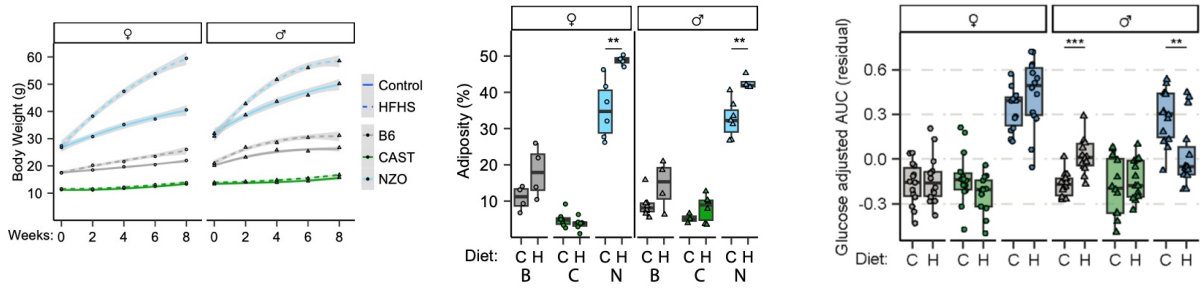
The Three Bears: a T2D Model



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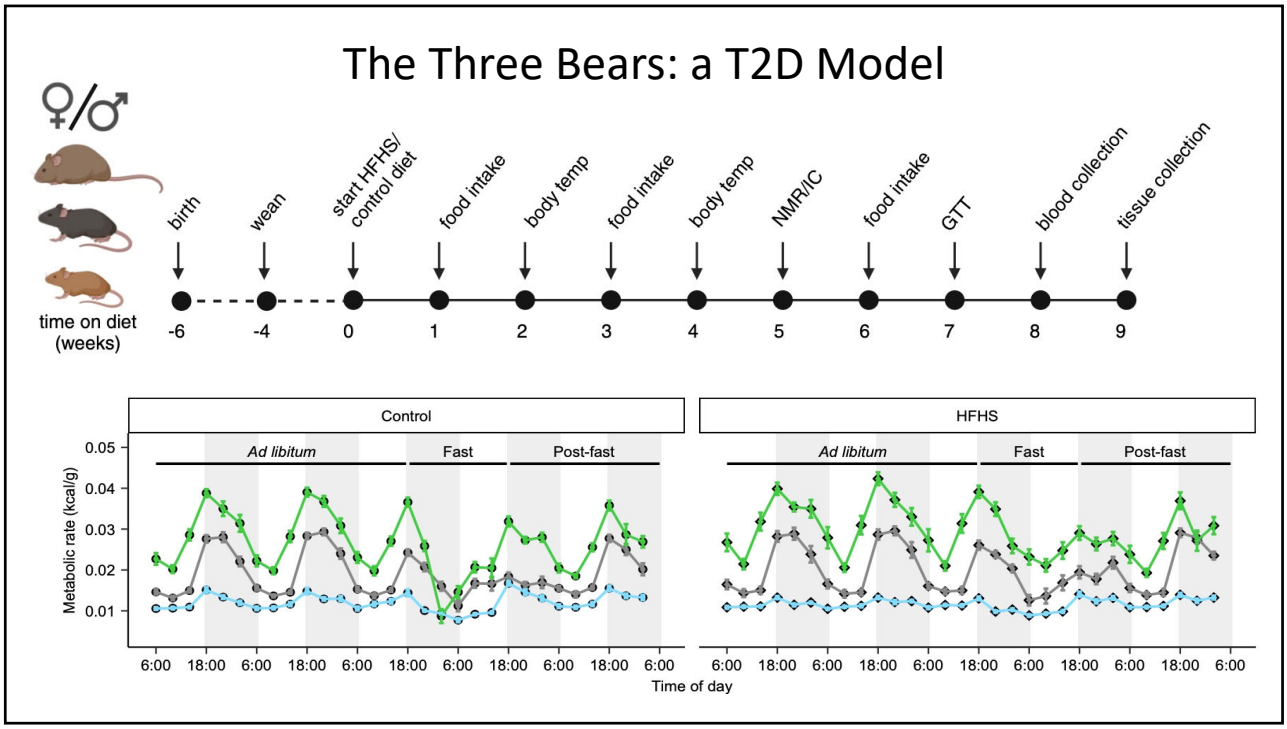
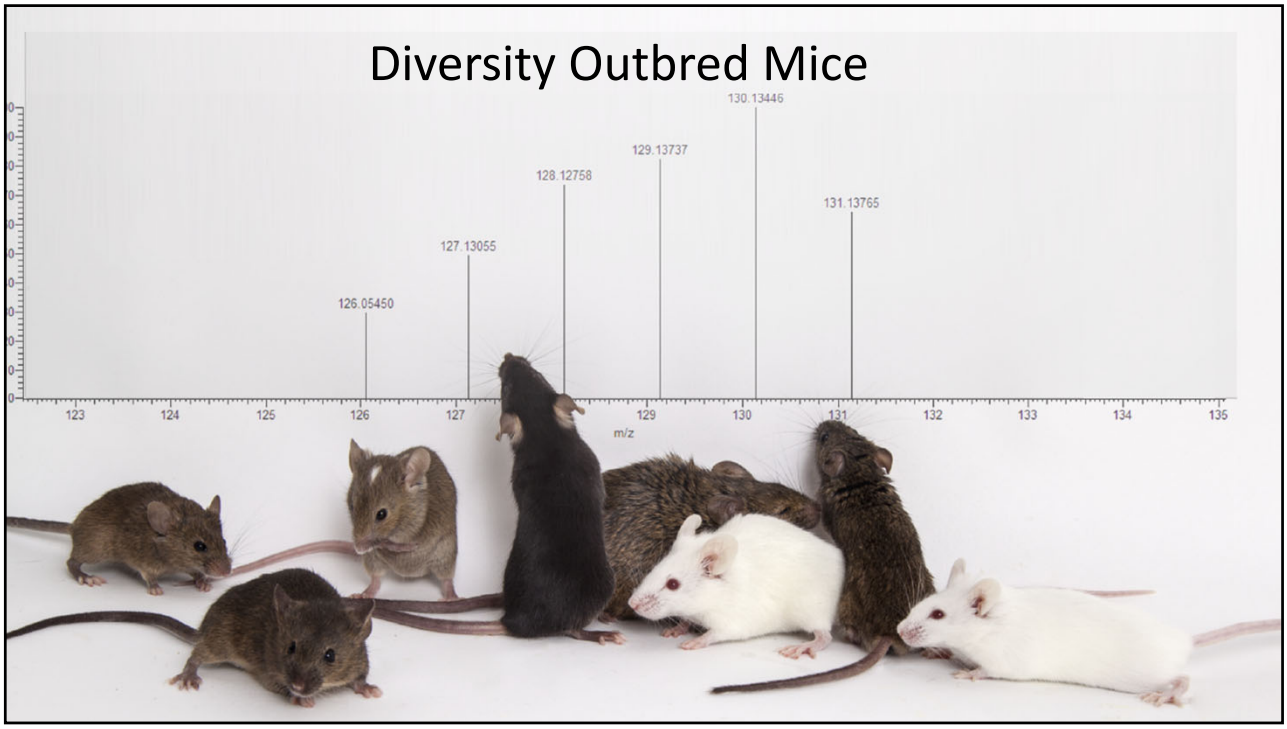

The Three Bears: a T2D Model
♀/♂
birth
wean
start HFHS/ control diet
food intake
body temp
food intake
body temp
NMR/IC
food intake
GTT
blood collection
tissue collection
time on diet (weeks)
-6
-4
0
1
2
3
4
5
6
7
8
9
Control
HFHS
Ad libitum
Fast
Post-fast
Metabolic rate (kcal/g)
0.05
0.04
0.03
0.02
0.01
6:00
18:00
Time of day

11


Diversity Outbred Mice
130.13446
129.13737
128.12758
131.13765
127.13055
126.05450
123
124
125
126
127
129
130
131
132
133
134
135
m/z

12

Dietary Interventions in Diversity Outbred Mice

Ad libitum

AL

3.43 g/day

Mo Tu We Th Fr Sa Sn

Unlimited amount of food

Caloric restriction

20% CR 40% CR

2.75 g/day 2.06 g/day

3x meal

Mo Tu We Th Fr Sa Sn

*Fed daily at 2pm

Intermittent fasting

No food for 24 (1D IF) or 48 (2D IF) consecutive hours per week

1DF Mo Tu We Th Fr Sa Sn

2DF Mo Tu We Th Fr Sa Sn

*Food added or removed at 2pm

DiFrancesco et al, 2024 Nature

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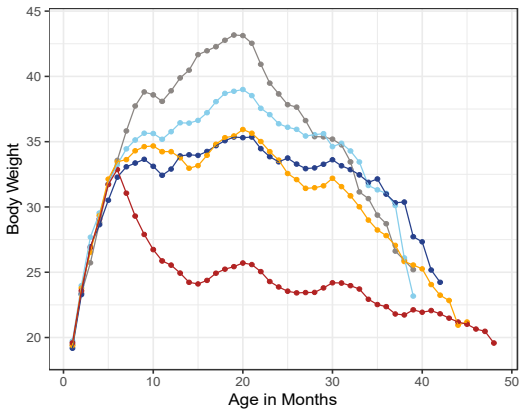
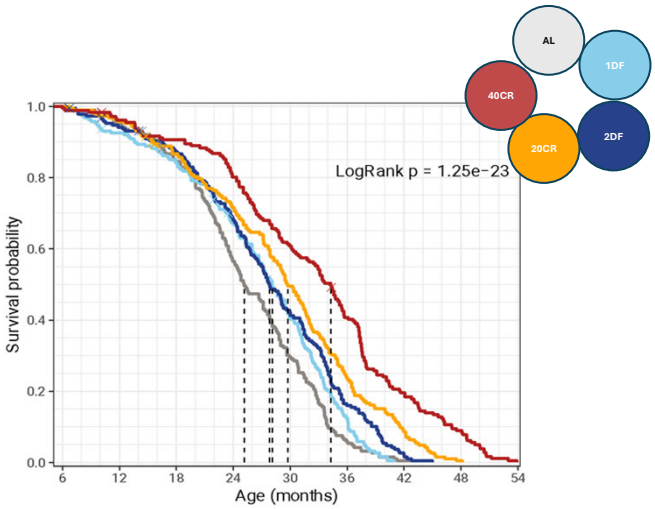
Dietary Interventions in Diversity Outbred Mice





DiFrancesco et al, 2024 Nature

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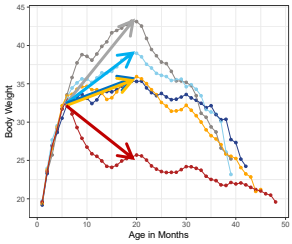
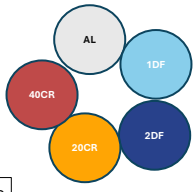
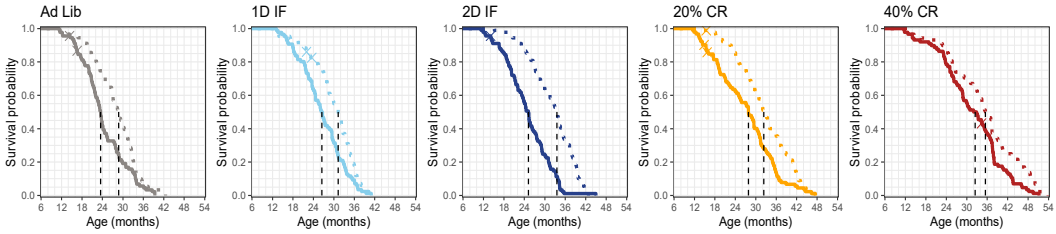
Dietary Interventions in Diversity Outbred Mice

Body weight loss is associated with shorter lifespan.





BW Change
Loss
Gain



DiFrancesco et al, 2024 Nature

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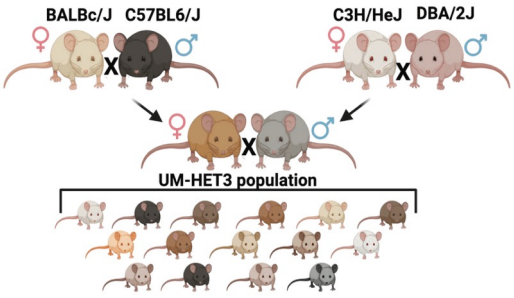
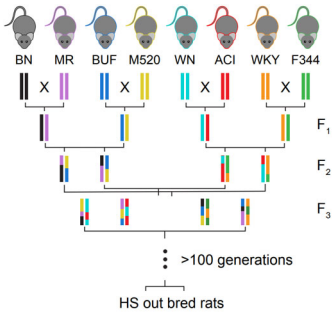
More Genetic Diversity Resources

NIA Interventions Testing Program (ITP)



Poudel et al. 2024 Arthritis Res Ther.

NIDA Heterogeneous Stock Rats



https://ratgenes.org

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Acknowledgements

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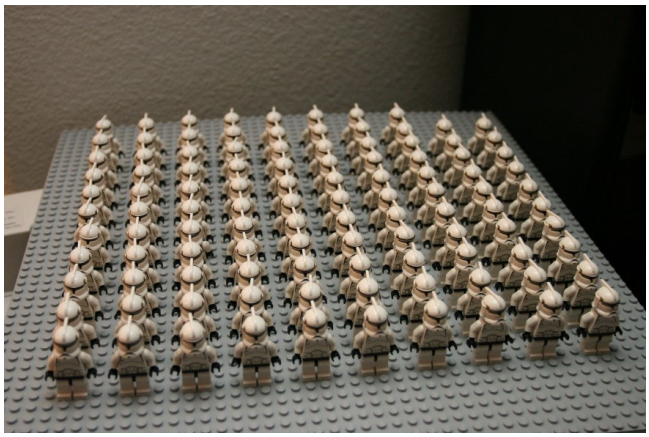
Questions?



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